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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/341,700	09/24/99	SCHLINGENSIEPEN K	P63763US0

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EXAMINER	
ZARA, J	
ART UNIT	**PAPER NUMBER**
1635	14

DATE MAILED: 08/28/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

F14

Office Action Summary

Application No.	Applicant(s)
09/341,700	Schlingensiepen et al
Examiner	**Group Art Unit**
Zara, Jane	1635

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-17* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8 and 9*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice To Comply

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-17 are pending in the instant application.

Specification

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. SEQ ID Nos. must accompany appropriate sequences which are disclosed in the figures and text of the specification (i.e. See especially claims 7 and 13). See the accompanying Notice to Comply. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Claim Objections

Claims 9-17 are objected to under 37 CFR 1.75© as being in improper form because they are multiple dependent claims which depend on multiple dependent claims . See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

The word "steroide" is misspelled in claim 6.

The word "ore" in line 6 and the words "indepently" and nueloetides" in line 8 are misspelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "elements" needs to be defined in claims 1 and 9.

The modifications which lead to the generation of higher nuclease resistance of oligonucleotides need to be further delineated in claim 3.

In claims 7 sand 13, the oligonucleotides need to be defined in terms which do not rely on the reference of a figure.

The term "derivative(s) thereof" needs to be defined in claims 8 and 12.

In claim 13, the term "as well as" renders the claim vague and indefinite, since it is not known which set or subset of sequences the claims are drawn to.

The term "additives" in claim 15 needs to be further defined.

Claims 16 and 17 provide for the use of oligonucleotides, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 16 and 17 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of gene expression *in vitro*, does not reasonably provide enablement for *in vivo* gene inhibition and treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions for the treatment of conditions and diseases involving cellular proliferation whereby the FosC, JunB and -D, p53, TGF-beta 1 and 2, erbB-2, and rb genes are inhibited in an organism and some kind of treatment effects are provided.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed. This determination is based on several factors which, when considered together, illustrate that the art

of gene delivery, expression and/or inhibition is in its infancy and highly unpredictable. The discussion is also based on references whose teachings show that, despite a tremendous amount of experimentation by highly skilled artisans in the field of gene delivery and expression *in vivo*, there remain significant hurdles known in the art to make and/or use the invention over the scope claimed.

The nature of the invention. Methods of targeting nucleic acids into host cell *in vivo* fall into the broad area known as gene therapy methods. While delivery of nucleic acids in and of itself is not considered as therapy per se, *in vivo* delivery shares many of the obstacles recognized for the actual therapy methods because successful therapy methods are for the most part based on the ability to deliver exogenous nucleic acids to cells or tissues of interest.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of gene delivery. Crystal points out that some advantages of using plasmid-liposome complexes as gene transfer vectors include their general inefficiency at achieving successful gene transfer and a general lack of available data regarding repetitive administration of liposomes of DNA to whole organisms (page 405, second paragraph). Schofield *et al* also teach advantages of liposome delivery of genes *in vivo*, although many of the details regarding cell targeting, cell entry and gene expression in target cells remain highly speculative. Schofield *et al* caution that there are *significant variations that exist between animals*, and state that only limited conclusions could be drawn from animal studies which may be applied to the treatment of humans (pages 61-64).

Verma *et al* teach the problems of gene delivery in whole organisms using non-viral vector approaches, including liposomes as delivery agents, and state that such approaches suffer from limitations relating to poor efficiency of delivery and the transient expression of delivered genes (page 239, second paragraph from the end). Friedmann teaches that gene transfer by liposomes is much less efficient than virus-mediated transfer (page 100, last paragraph-page 101, first paragraph), while, according to Friedmann, the gene therapy field as a whole currently lacks convincing therapeutic benefit (page 96). Branch and Crooke teach that the *in vivo* (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke).

While these references acknowledge the usefulness of gene therapy including lipid mediated delivery and the possibility of developing efficacious strategies in the future, they also illustrate that there are numerous obstacles to successful gene therapy which current methods still must overcome. As such, the disclosed utilities of the present specification which are drawn to gene delivery methods are credible. The present rejection, therefore is not for lack of utility, but rather for lack of enablement for the methods claimed.

The amount of direction or guidance presented in the specification and the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of treating conditions and diseases involving cellular proliferation whereby the

FosC, JunB and -D, p53, TGF-beta 1 and 2, erbB-2, and rb genes are inhibited in an organism and some kind of treatment effects are provided.

The specification teaches the *in vitro* inhibition of various target genes using antisense. The specification fails to teach the successful delivery of antisense and subsequent inhibition of appropriate target genes involved in cellular proliferation in a whole organism whereby treatment effects are provided. One skilled in the art would not accept on its face the examples given in the specification of target gene inhibition as being correlative or representative of the administration of antisense in any and/or all organisms such that the appropriate genes involving cellular proliferation are inhibited and further where treatment is provided in view of the lack of guidance in the specification and known unpredictability associated with the administration and *in vivo* delivery of antisense. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant target genes.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to compositions for the treatment of conditions and diseases involving cellular proliferation whereby the FosC, JunB and -D, p53, TGF-beta 1 and 2, erbB-2, and rb genes are inhibited and some kind of treatment effects are provided in any organism comprising the administration of antisense via any route of administration to any organism. In order to practice the invention over the scope claimed, it

would require trial and error or undue experimentation beyond which is taught in the specification to practice the invention drawn to any route of administration of an antisense to an organism such that the appropriate target genes are inhibited and further where treatment effects are provided. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cell and /or tissues harboring the target genes such that the genes are inhibited *in vivo* and further that treatment effects are provided. Since the specification fails to provide any particular guidance for the successful delivery of antisense in any organisms, and since determination of these factors for a particular antisense in a particular organism with a particular condition or disease involving cellular proliferation is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Milner *et al* and James in view of the combination of Vaerman *et al* and Ehrlich *et al*.

The claims are drawn to antisense oligonucleotides and methods of preparing them, which methods comprise a determination of the amounts of consecutive groups of cytosine or inosine bases relative to the base constitution of the entire oligonucleotide sequence whereby the ratio between those bases which comprise 3 hydrogen bonds for their target sequence divided by those which have a combination of 3 hydrogen bonds and two hydrogen bonds for their target sequences is greater than or equal to 0.29, which oligonucleotides may further comprise phospholipids or steroid hormones, and which may further comprise base, sugar or internucleoside modifications for enhanced nuclease stability.

Milner *et al* and James teach methods of selecting effective antisense reagents to target genes of known sequences, which oligonucleotides may further comprise nuclease stabilizing sugar, base or internucleoside modifications, and which oligonucleotide compositions may further comprise lipids (See entire text of Milner *et al*, especially figure 3, page 539. See entire text of James, especially pages 197-198).

The primary references do not teach cellular cytotoxicity of antisense in relation to specific cytosine (or inosine) content or configurations.

Vaerman *et al* teach antiproliferative effects of antisense oligonucleotides comprising both target gene inhibition and toxicity due to the content and configuration of cytosine residues within the oligonucleotides (See entire text, especially abstract and introduction, page 331; tables 1-5 and figure 1).

Ehrlich *et al* teach methods of distinguishing between sequence dependent and non-specific effects exerted by antisense oligonucleotides, which modifications include phosphorothioate internucleoside linkages (abstract and introduction, pages 173-174; figure 1, page 175; figure 3, page 177).

It would have been obvious to one of ordinary skill in the art to determine methods of selecting effective antisense which target genes of known sequence, because this had been taught previously by Milner *et al* and James. One of ordinary skill in the art would have been motivated to target genes involved in cellular proliferation, because the role of numerous genes including Fos, Jun, erb, p53 had been taught routinely in the art, and the motivation to inhibit gene expression using antisense had been taught previously by the Milner *et al*, James, Ehrlich *et al* and Vaerman *et al*. One of ordinary skill in the art would have expected that antisense exert their effects in both a non-specific and sequence specific way, as taught previously by Ehrlich *et al* and Vaerman *et al*, which non-specific effects have been observed in *in vitro* cellular toxicity studies, and which toxicity has been correlated to cytosine content and configuration, as taught

previously by Vaerman *et al*. Furthermore, one of ordinary skill in the art would have been motivated to reduce toxicity effects of antisense by reducing the number of consecutive cytosine residues in an antisense construct because the correlation between cytosine content and cytotoxicity have been taught by Vaerman *et al*, and modifications such as phosphorothioate internucleoside linkage substitution ~~have~~ HAS been shown previously by Vaerman *et al* and by Ehrlich *et al* to enhance stability and cellular targeting of antisense, while reducing cellular toxicity of target cells by antisense, whereby antisense oligonucleotides have been administered to cells *in vitro* in compositions further comprising lipids.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

August 18, 2000

REMY YUCEL, PH.D
PRIMARY EXAMINER